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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,521	02/15/2000	PETER E. NIELSEN	ISIS-3070	8096

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/424,521	NIELSEN, PETER E.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-27,31-34,38-41,45-48 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23-27,31-34,38-41,45-48 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed August 28, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed July 2, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. Applicant's arguments with respect to the enablement rejection of record against claims 39-41, 45-48, and 52 have been considered. Said enablement rejection is maintained for reasons of record, and the Office response to applicants' arguments is set forth towards the end of this rejection. Furthermore, the following new references are cited in support of the instant rejection, and claims 21, 25-27, 31-34 and 38 are newly rejected under this statute for the reasons given below.

Claims 21, 25-27, 31-34, 38-41, 45-48, and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of CAT expression *in vitro*, does not reasonably provide enablement for antisense-mediated modulation of protein expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of modulating the cellular uptake and distribution of a peptide nucleic acid (PNA) in cells or tissues, comprising conjugating said PNA with a lipid, alkyl, or steroid, introducing the conjugated PNA into liposomes, and contacting a cell with the PNA conjugate. The claims of the above invention are also drawn to methods of modulating gene expression in an animal comprising administering a therapeutically effective amount of a PNA composition. The language of such claims clearly encompasses *in vivo* activity. The specification exemplifies the synthesis of such PNA oligos, and also exemplifies a method of using the claimed compositions to inhibit the expression of CAT in HeLa cells *in vitro*. The specification prophetically considers general treatment regimens and therapeutic uses for such PNA compositions.

The specification as filed is not considered to provide adequate guidance or examples that would enable a skilled artisan to use the claimed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the activity of a PNA compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers general

methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of the art of PNA-mediated gene inhibition *in vivo* is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the unpredictable nature of the *in vivo* use of antisense compounds. While such articles discuss several types of nucleic acid based therapeutics in addition to PNA's, a reading of the articles as a whole indicates that the problems in the art that contribute to the overall unpredictability of using such compounds *in vivo* are considered to apply to all such nucleic acid based therapeutics.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art of nucleic acid-based gene inhibitors: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos,

toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis".

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The common theme running through all of these articles is that even in those relatively rare instances where *in vivo* success with a given compound has occurred, such events are clearly the exception rather than the rule. Furthermore, it is maintained here that such success cannot be forecasted *a priori*, because none of the articles describe how to overcome the problems that are well-documented in said references (i.e those relating to target site access, cellular delivery and uptake, toxicity and immunological problems, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins). Although a few cited references describe some compounds as having *in vivo* activity, no predictable mechanism is set forth in any such

reference that would allow one of skill to know whether any new compounds would have *in vivo* activity, other than to engage in undue trial and error experimentation. Furthermore, the specification of the instant application fails to resolve any of these outstanding issues and provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Special attention is directed to the scope of applicants' claim language drawn to *modulation* of gene expression, since such language encompasses both inhibition and upregulation of gene expression. The specification fails to teach any instance of PNA-mediated gene upregulation at all. Furthermore, the examiner was unable to locate any references teaching the use of PNA's to stimulate gene transcription, and thus the art appears to be silent as to the use of such PNA compounds in methods of upregulating gene expression. For this reason alone, given the unpredictability of using the claimed compounds in gene upregulation, which contradicts the teachings of applicants specification drawn to gene inhibition, and since such teachings of PNA-mediated gene upregulation apparently do not find a basis in the art, one of skill would necessarily have to engage in undue trial and error experimentation in order to practice the full scope of applicants claimed invention drawn to modulating gene expression.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations that are successfully delivered to target sites in appropriate cells and /or tissues. In the absence of any real guidance from the

specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

5. Most of applicants arguments regarding this rejection are believed to be addressed in the rejection as restated above. However, applicants arguments as they may pertain to this rejection are not considered convincing. Applicants understanding of the instant rejection appears to be misconstrued, since such arguments appear to be directed towards the assertion that the instant rejection is based on a lack of knowledge regarding the extent of therapeutic benefit that would be provided by the instant methods. Applicants appear to assert that they need not be enabled for any therapeutic benefit, and allege that "[i]ndeed, Applicants do not claim a particular level of activity. Rather, their claims are directed to methods for simply modulating gene expression." Applicants later argue that "[t]here is no reason to believe that one skilled in the art would be required to perform any amount of undue experimentation to administer the claimed compounds to a subject and achieve some measurable effect". In response, applicants are referred to their own claim language, (e.g. claims 39 and 46) which require that the dose of PNA to be delivered be "therapeutically effective". Since this is clearly a higher level than "simply modulating gene expression" or "some measurable effect" as stated in their arguments, such arguments are not applicable.

Furthermore, since a level of activity is recited in the claims, this would in fact would be one aspect considered in the analysis of enablement, particularly if the lack of knowledge regarding the extent of therapeutic benefit would lead to a conclusion that such a benefit would be unpredictably achieved. It is maintained here that the extent of any such benefit is unpredictable. This view finds support in the cited references above, which detail the extent of

uncertainty of using such compounds to achieve any therapeutic end, and also from the specification which fails to exemplify any living or analogous system.

Regarding applicants allegation that the instant rejection "appears to be resurrecting a stringent requirement of therapeutic utility that was unambiguously rejected by the PTO many years ago," applicants are reminded that this is not a rejection under 35 U.S.C. § 101 Utility, and the applicability of arguments pertaining thereto is not clear. Enablement requires that the application teach how to make and use the invention without undue experimentation, and as set forth above, there is substantial reason to believe that one skilled in the art would be required to perform undue experimentation to practice the invention as claimed.

Finally, Applicants' assert that the specification provides more than ample illustrative examples to meet the enablement standard, because the specification describes administration and dosing of the instantly claimed compounds at page 15 through page 18. However, a review of these sections finds nothing more than generically recited and prophetic dosages that apply to virtually any therapeutic compound ever made. For example, page 15 lines 14-18 recite that "Depending on the frequency of administration, ranging from daily to monthly, and the dose to be administered, ranging from 0.01 μg to 100 g per kg of body weight the pump reservoir may be refilled at 3-10 week intervals." One of skill in the art would understand that such alleged guidance applies to most compounds, and conversely, that no one compound or class of compounds is effective within this diversity of ranges. Such thus arguments are not considered convincing, and the rejection is maintained.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23 and 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,773,571. Although the conflicting claims are not identical, they are not patentably distinct from each other because the structure of instant claims 23 and 24 is embraced by the structure of claim 1 of U.S. Patent No. 5,773,571, because the generic structure of claim 1 of U.S. Patent No. 5,773,571 teaches all the elements at all the same positions of the molecule of claims 23 and 24 of the instant application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD

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